

Amendments to the Claims

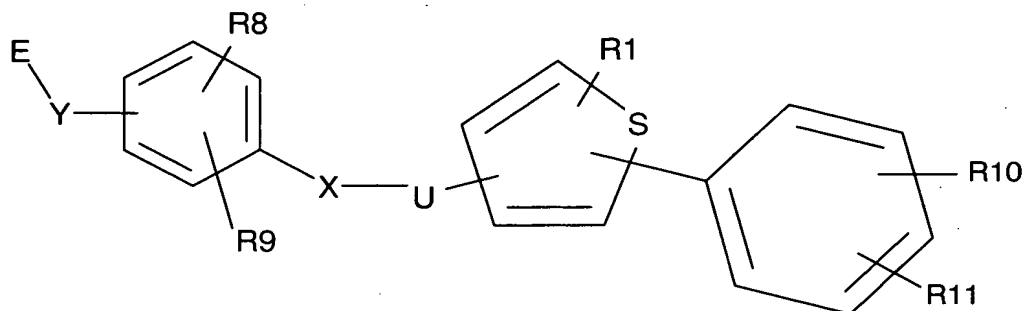
Please cancel claims: 45, 49, 59, and 60.

In the Claims

This listing of claims will replace all prior versions and listings of claims in the application.

What is claimed is:

1. (Original) A compound of the Formula I':



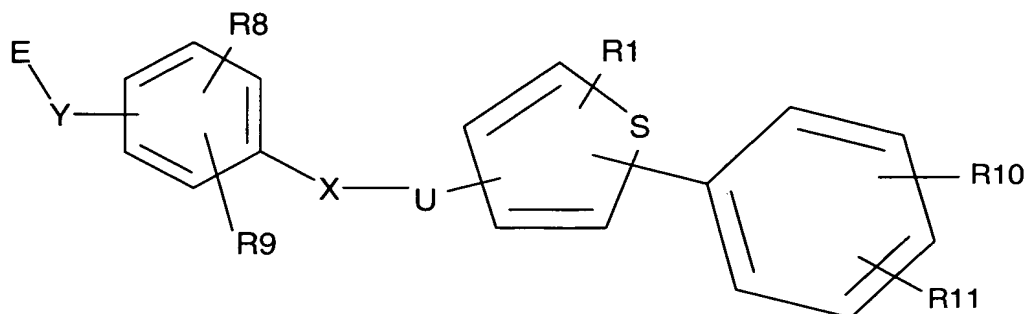
and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- (a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, phenyl, aryl-C₁₋₄-heteroalkyl, heteroaryl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₈ alkyl is optionally substituted with from one to three substituents independently selected from R1'; and further wherein C₁-C₈ alkenyl, phenyl, aryl-C₁₋₄-heteroalkyl, heteroaryl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, are each optionally substituted with from one to three substituents independently selected from R2;
- (b) R1' are each independently selected from the group consisting of hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₁₋₄-alkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂; R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄ and R₂₅ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;

- (c) R2, R26, R27, R28, and R31 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂;
- (d) X is selected from the group consisting of O, S, S(O)₂, N and a bond;
- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R₃₀;
- (f) Y is selected from the group consisting of C, NH, and a single bond;
- (g) E is C(R₃)(R₄)A or A and wherein
 - (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;
 - (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
 - (iii) R₃ is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
 - (iv) R₄ is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R₃ and R₄ are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R₂₆; with the proviso that when R₁ is C₁-C₈ alkyl, Y is in a para substituted position with relation to X, and X is selected from the group consisting of a bond and O, then R₄ is selected from the group consisting of C₁-C₅ alkoxy, aryloxy, and arylC₀-C₄ alkyl; with the additional proviso that when R₁ is C₁-C₈ alkyl, Y is in a para substituted position with relation to X, X is S, and U is optionally

substituted methylene, then R4 is selected from the group consisting of C₁-C₅ alkoxy, aryloxy, and aryl-C₀-C₄ alkyl;

- (h) R8 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
 - (i) R9 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR29, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C₁-C₄ alkyl;
 - (j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR12'', C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', OS(O)₂R16', N(R17')₂, NR18'C(O)R19', NR20'SO₂R21', SR22', S(O)R23', S(O)₂R24', and S(O)₂N(R25')₂; and wherein aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R28;
 - (k) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl; and
 - (l) R30 is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R31.
2. (Original) A compound of the Formula I':



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

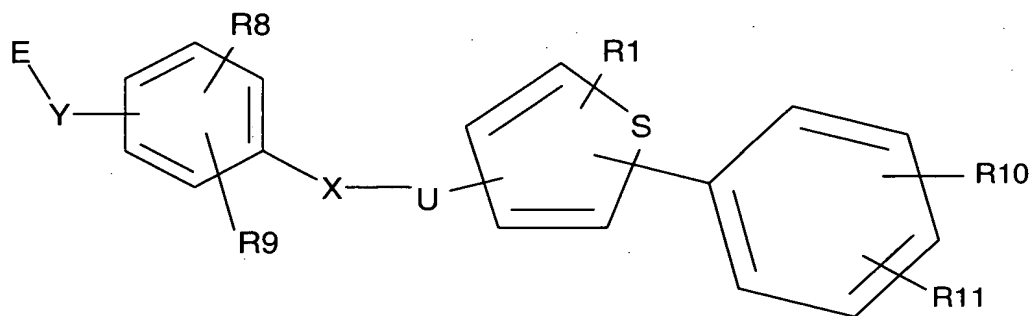
- (a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, phenyl, aryl-C₁₋₄-heteroalkyl, heteroaryl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₈ alkyl is optionally substituted with from one to three substituents independently selected from R1'; and further wherein C₁-C₈ alkenyl, phenyl, aryl-C₁₋₄-heteroalkyl, heteroaryl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, are each optionally substituted with from one to three substituents independently selected from R2;
- (b) R1' are each independently selected from the group consisting of hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₁₋₄-alkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂; R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄ and R₂₅ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (c) R₂, R₂₆, R₂₇, R₂₈, and R₃₁ are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂;
- (d) X is selected from the group consisting of O, S, S(O)₂, N and a bond;

- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is substituted with from one to four substituents each independently selected from R30;
- (f) Y is selected from the group consisting of C, O, S, NH and a single bond;
- (g) E is C(R3)(R4)A or A and wherein
 - (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;
 - (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
 - (iii) R3 is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
 - (iv) R4 is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R3 and R4 are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R26; with the proviso that when R1 is C₁-C₈ alkyl, Y is in a para substituted position with relation to X, and X is selected from the group consisting of a bond and O, then R4 is selected from the group consisting of C₁-C₅ alkoxy, aryloxy, and arylC₀-C₄ alkyl; with the additional proviso that when R1 is C₁-C₈ alkyl, Y is in a para substituted position with relation to X, X is S, and U is optionally substituted methylene, then R4 is selected from the group consisting of C₁-C₅ alkoxy, aryloxy, and arylC₀-C₄ alkyl;
- (h) R8 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
- (i) R9 is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR29, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from

one to three independently selected from R27; R29 is selected from the group consisting of hydrogen and C₁-C₄ alkyl;

- (j) R10, R11 are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR12'', C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R13', COOR14', OC(O)R15', OS(O)₂R16', N(R17')₂, NR18'C(O)R19', NR20'SO₂R21', SR22', S(O)R23', S(O)₂R24', and S(O)₂N(R25')₂; and wherein aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R28;
- (k) R12', R12'', R13', R14', R15', R16', R17', R18', R19', R20', R21', R22', R23', R24', and R25' are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl; and
- (l) R30 is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R31.

3. (Original) A compound of the Formula I''':



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

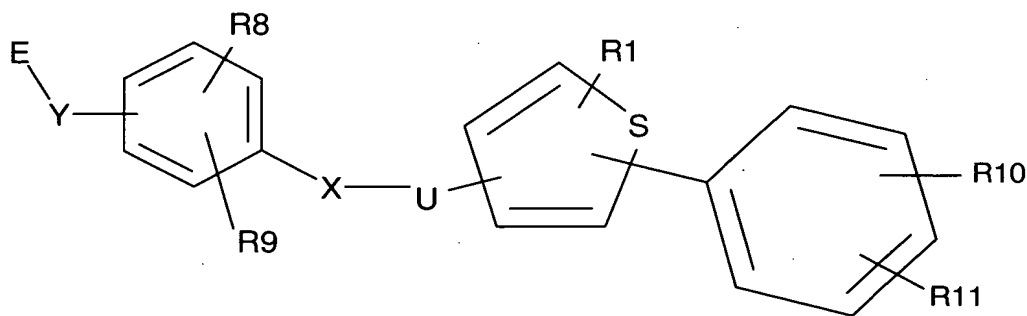
- (a) R1 is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, phenyl, aryl-C₁₋₄-heteroalkyl, heteroaryl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₈ alkyl is optionally substituted with from one to three substituents independently selected from R1'; and further wherein C₁-C₈ alkenyl, phenyl, aryl-C₁₋₄-heteroalkyl, heteroaryl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, are each optionally substituted with from one to three substituents independently selected from R2;
- (b) R1' are each independently selected from the group consisting of hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₁₋₄-alkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂; R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄ and R₂₅ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (c) R₂, R₂₆, R₂₇, R₂₈, and R₃₁ are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂;
- (d) X is selected from the group consisting of O, S, S(O)₂, N and a bond;
- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker is optionally replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with from one to four substituents each independently selected from R₃₀;
- (f) Y is selected from the group consisting of C, O, S, NH and a single bond;
- (g) E is C(R₃)(R₄)A or A and wherein
 - (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;

- (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀-C₄ alkyl and C₁-C₆ alkyl;
- (iii) R₃ is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
- (iv) R₄ is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R₃ and R₄ are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R₂₆; with the proviso that when R₁ is C₁-C₈ alkyl, Y is in a para substituted position with relation to X, and X is selected from the group consisting of a bond and O, then R₄ is selected from the group consisting of C₁-C₅ alkoxy, aryloxy, and arylC₀-C₄ alkyl; with the additional proviso that when R₁ is C₁-C₈ alkyl, Y is in a para substituted position with relation to X, X is S, and U is optionally substituted methylene, then R₄ is selected from the group consisting of C₁-C₅ alkoxy, aryloxy, and arylC₀-C₄ alkyl; with the further proviso that when Y is O then R₄ is selected from the group consisting of C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and R₃ and R₄ are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R₂₆;
- (h) R₈ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
- (i) R₉ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR₂₉, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R₂₇; R₂₉ is selected from the group consisting of hydrogen and C₁-C₄ alkyl;
- (j) R₁₀, R₁₁ are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂'', C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇

cycloalkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C3-C6 cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R_{13'}, COOR_{14'}, OC(O)R_{15'}, OS(O)₂R_{16'}, N(R_{17'})₂, NR_{18'}C(O)R_{19'}, NR_{20'}SO₂R_{21'}, SR_{22'}, S(O)R_{23'}, S(O)₂R_{24'}, and S(O)₂N(R_{25'})₂; and wherein aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C3-C6 cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R₂₈;

- (k) R_{12'}, R_{12''}, R_{13'}, R_{14'}, R_{15'}, R_{16'}, R_{17'}, R_{18'}, R_{19'}, R_{20'}, R_{21'}, R_{22'}, R_{23'}, R_{24'}, and R_{25'} are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl; and
- (l) R₃₀ is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C3-C6 cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl- C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C3-C6 cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R₃₁.

4. (Original) A compound of the Formula I:



and stereoisomers, pharmaceutically acceptable salts, solvates and hydrates thereof, wherein:

- (a) R₁ is selected from the group consisting of hydrogen, C₁-C₈ alkyl, C₁-C₈ alkenyl, phenyl, aryl-C₁₋₄-heteroalkyl, heteroaryl, and C3-C6 cycloalkylaryl-C₀₋₂-alkyl, and wherein C₁-C₈ alkyl is optionally substituted with from one to three substituents independently selected from R_{1'}; and further wherein C₁-

C₈ alkenyl, phenyl, aryl-C₁₋₄-heteroalkyl, heteroaryl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, are each optionally substituted with from one to three substituents independently selected from R₂;

- (b) R₁' are each independently selected from the group consisting of hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₁₋₄-alkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂; R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄ and R₂₅ are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl;
- (c) R₂, R₂₆, R₂₇, R₂₈, and R₃₁ are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR₁₂, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryloxy, aryl-C₀₋₄-alkyl, heteroaryl, heterocycloalkyl, C(O)R₁₃, COOR₁₄, OC(O)R₁₅, OS(O)₂R₁₆, N(R₁₇)₂, NR₁₈C(O)R₁₉, NR₂₀SO₂R₂₁, SR₂₂, S(O)R₂₃, S(O)₂R₂₄, and S(O)₂N(R₂₅)₂;
- (d) X is selected from the group consisting of O, S, S(O)₂, N, and a bond;
- (e) U is an aliphatic linker wherein one carbon atom of the aliphatic linker may be replaced with O, NH or S, and wherein such aliphatic linker is optionally substituted with R₃₀;
- (f) Y is selected from the group consisting of C, O, S, NH and a single bond;
- (g) E is C(R₃)(R₄)A or A and wherein
 - (i) A is selected from the group consisting of carboxyl, tetrazole, C₁-C₆ alkylnitrile, carboxamide, sulfonamide and acylsulfonamide; wherein sulfonamide, acylsulfonamide and tetrazole are each optionally substituted with from one to two groups independently selected from R⁷;
 - (ii) each R⁷ is independently selected from the group consisting of hydrogen, C₁-C₆ haloalkyl, aryl C₀₋₄ alkyl and C₁-C₆ alkyl;
 - (iii) R₃ is selected from the group consisting of hydrogen, C₁-C₅ alkyl, and C₁-C₅ alkoxy; and
 - (iv) R₄ is selected from the group consisting of H, C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀₋₄ alkyl, and R₃ and R₄

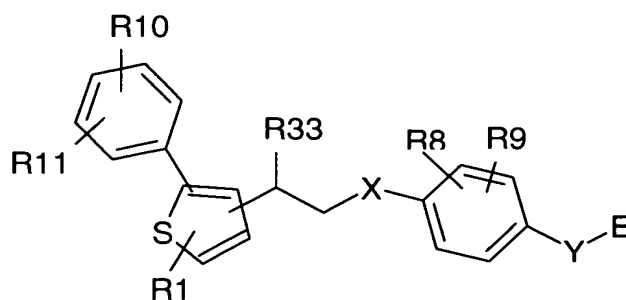
are optionally combined to form a C₃-C₄ cycloalkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R₂₆; with the proviso that when R₁ is C₁-C₈ alkyl, Y is in a para substituted position with relation to X, and X is selected from the group consisting of a bond and O, then R₄ is selected from the group consisting of C₁-C₅ alkoxy, aryloxy, and arylC₀-C₄ alkyl; with the additional proviso that when R₁ is C₁-C₈ alkyl, Y is in a para substituted position with relation to X, X is S, and U is optionally substituted methylene, then R₄ is selected from the group consisting of C₁-C₅ alkoxy, aryloxy, and arylC₀-C₄ alkyl;

- (h) R₈ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, and halo;
- (i) R₉ is selected from the group consisting of hydrogen, C₁-C₄ alkyl, C₁-C₄ alkylenyl, halo, aryl-C₀-C₄ alkyl, heteroaryl, C₁-C₆ allyl, and OR₂₉, and wherein aryl-C₀-C₄ alkyl, heteroaryl are each optionally substituted with from one to three independently selected from R₂₇; R₂₉ is selected from the group consisting of hydrogen and C₁-C₄ alkyl;
- (j) R₁₀, R₁₁ are each independently selected from the group consisting of hydrogen, hydroxy, cyano, nitro, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR_{12''}, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkyloxy, C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, aryloxy, C(O)R_{13'}, COOR_{14'}, OC(O)R_{15'}, OS(O)₂R_{16'}, N(R_{17'})₂, NR_{18'}C(O)R_{19'}, NR_{20'}SO₂R_{21'}, SR_{22'}, S(O)R_{23'}, S(O)₂R_{24'}, and S(O)₂N(R_{25'})₂; and wherein aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three independently selected from R₂₈;
- (k) R_{12'}, R_{12''}, R_{13'}, R_{14'}, R_{15'}, R_{16'}, R_{17'}, R_{18'}, R_{19'}, R_{20'}, R_{21'}, R_{22'}, R_{23'}, R_{24'}, and R_{25'} are each independently selected from the group consisting of hydrogen, C₁-C₆ alkyl and aryl; and
- (l) R₃₀ is selected from the group consisting of C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋

2-alkyl, and wherein C₁-C₆ alkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, and C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl are each optionally substituted with from one to three substituents each independently selected from R₃₁.

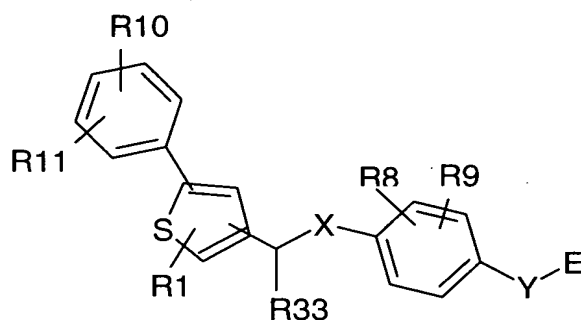
5. Original) A compound as claimed by any one of Claims 1 through 4 wherein X is -O-.
6. (Original) A compound as claimed by any one of Claims 1 through 4 wherein X is -S-.
7. (Currently amended) A compound as claimed by ~~any one of~~ Claims 1 through 6 wherein R₄ is selected from the group consisting of C₁-C₅ alkoxy, aryloxy, and arylC₀-C₄ alkyl.
8. (Currently amended) A compound as claimed by ~~any one of~~ Claims 2 through 7 wherein Y is O.
9. (Currently amended) A compound as claimed by ~~any one of~~ Claims 1 through 7 wherein Y is C.
10. (Currently amended) A compound as claimed by ~~any one of~~ Claims 1 through 7 wherein Y is S.
11. (Currently amended) A compound as claimed by any one of Claims 1 through ~~10~~ 4 wherein E is C(R₃)(R₄)A.
12. (Currently amended) A compound as claimed by ~~any one of~~ Claims 1 through 11 wherein A is carboxyl.
13. (Currently amended) A compound as claimed by ~~any one of~~ Claims 1 through 12 2 wherein R₁ is H.
14. (Currently amended) A compound as claimed by ~~any one of~~ Claims 1 through 12 13 wherein A is COOH and R₁ is H.
15. (Currently amended) A compound as claimed by ~~any one of~~ Claims 1 through 14 wherein R₁₀ is haloalkyl.
16. (Currently amended) A compound as claimed by ~~any one of~~ Claims 1 through 15 11 wherein R₁₀ is CF₃.
17. (Currently amended) A compound as claimed by ~~any one of~~ Claims 1 through 14, wherein R₁₀ is haloalkyloxy.
18. (Currently amended) A compound as claimed by ~~any one of~~ Claims 1 through 17 5 wherein R₁₀ and R₁₁ are each independently selected from

- the group consisting of hydrogen, halo, oxo, C₁-C₆ alkyl, C₁-C₆ alkyl-COOR¹², C₁-C₆ alkoxy, C₁-C₆ haloalkyl, and C₁-C₆ haloalkyloxy.
19. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 14~~ 5 wherein R₁₀ is selected from the group consisting of C₃-C₇ cycloalkyl, aryl-C₀₋₄-alkyl, aryl-C₁₋₄-heteroalkyl, heteroaryl-C₀₋₄-alkyl, C₃-C₆ cycloalkylaryl-C₀₋₂-alkyl, and aryloxy.
 20. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 19~~ 5 wherein R₈ and R₉ are each independently selected from the group consisting of hydrogen and C₁-C₃ alkyl.
 21. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 20~~ 5 wherein R₃, and R₄ are each independently selected from the group consisting of C₁-C₂ alkyl.
 22. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 20~~ 11 wherein R₃, and R₄ are each independently selected from the group consisting of hydrogen and C₁-C₂ alkyl.
 23. (Currently amended) A compound as claimed by ~~any one of Claims 6 through 22~~, wherein X-U is optionally substituted -S(CH₂)₂.
 24. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 23~~ 11 wherein U is C₁-C₃ alkyl.
 25. (Original) A compound as claimed by Claim 24 wherein U is saturated.
 26. (Currently amended) A compound as claimed by ~~any one of Claims 1, 2, 3, 4, 23, 24, or 25~~ wherein U is substituted with C₁-C₃ alkyl.
 27. (Currently amended) A compound as claimed by ~~any one of Claims 1, 2, 3, 4, 23, 24, or 25~~ wherein U is substituted with arylC₁-C₄alkyl.
 28. (Currently amended) A compound as claimed by ~~any one of Claims 23, 24, 25, 26, or 27~~ wherein one carbon of the U group is replaced with an -O-.
 29. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 28~~ 11 wherein R₁ is selected from the group consisting of phenyl and pyridyl.
 30. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 22, or 29~~ 11 represented by the following Structural Formula II:



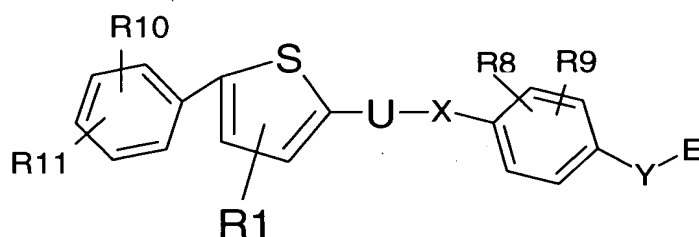
wherein R33 is selected from the group consisting of hydrogen, C₁-C₃ alkyl, and arylC₀-C₄ alkyl.

31. (Original) A compound as claimed by Claim 30 wherein R33 is arylC₁-C₄ alkyl.
32. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 22, or 29~~ 11 represented by the following Structural Formula III:

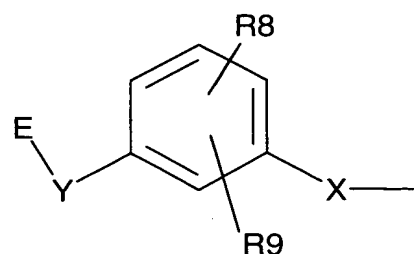


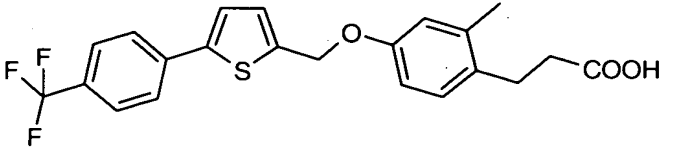
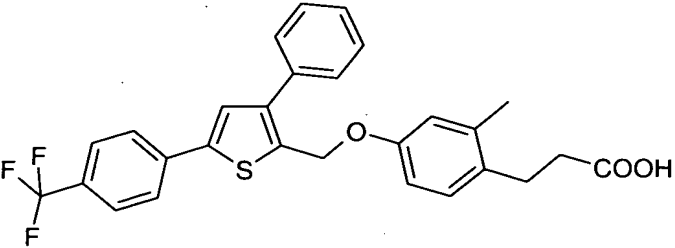
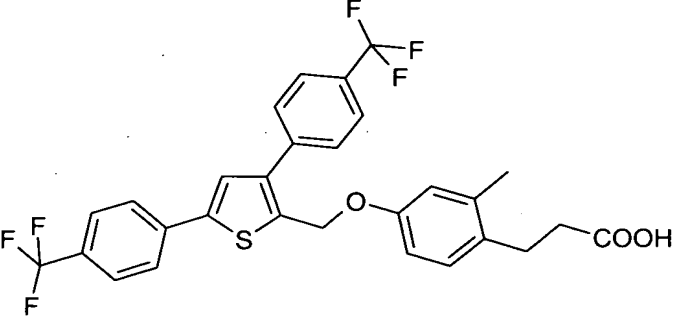
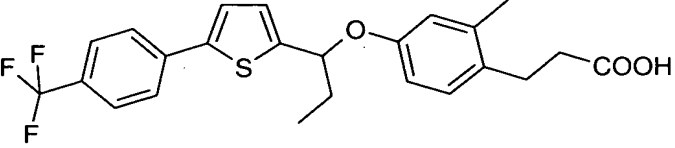
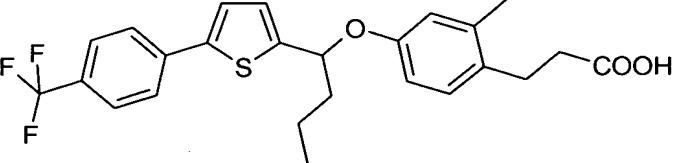
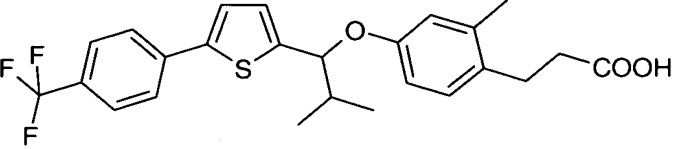
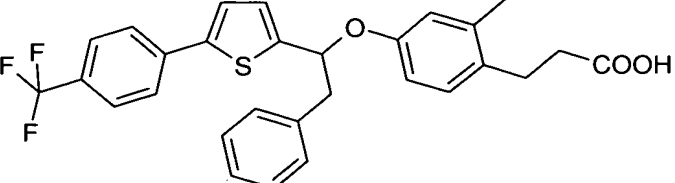
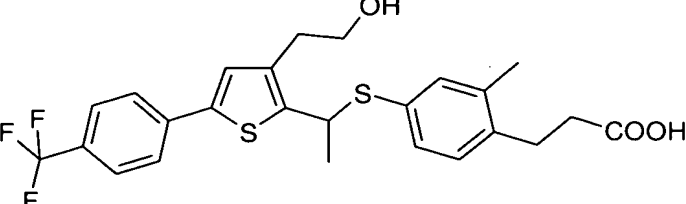
R33 is selected from the group consisting of hydrogen, C₁-C₃ alkyl, and arylC₀-C₄ alkyl.

33. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 29~~ 11 represented by the following Structural Formula IV:



34. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 29~~ 11 wherein the headpiece of Formula I is:



| Compound | Name |
|---|--|
|  | 3-{2-Methyl-4-[5-(4-trifluoromethyl-phenyl)-thiophen-2-ylmethoxy]-phenyl}-propionic acid |
|  | 3-{2-Methyl-4-[3-phenyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-ylmethoxy]-phenyl}-propionic acid |
|  | 3-{4-[3,5-Bis-(4-trifluoromethyl-phenyl)-thiophen-2-ylmethoxy]-2-methyl-phenyl}-propionic acid |
|  | 3-(2-Methyl-4-{1-[3-methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propoxy}-phenyl)-propionic acid |
|  | 3-(2-Methyl-4-{1-[3-methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-butoxy}-phenyl)-propionic acid |
|  | 3-(2-Methyl-4-{2-methyl-1-[3-methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propoxy}-phenyl)-propionic acid |
|  | 3-(2-Methyl-4-{1-[3-methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-2-phenyl-ethoxy}-phenyl)-propionic acid |
|  | 3-(4-{1-[3-(2-Hydroxyethyl)-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-ethylsulfanyl}-2-methyl-phenyl)-propionic acid |

35. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 34~~ 11 wherein R4 is selected from the group consisting of C₁-C₅ alkyl, C₁-C₅ alkoxy, aryloxy, C₃-C₆ cycloalkyl, and aryl C₀-C₄ alkyl, and wherein alkyl, alkoxy, cycloalkyl and aryl-alkyl are each optionally substituted with one to three each independently selected from R26.
36. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 35~~ 5 wherein E is C(R3)(R4)A.
37. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 35~~ 6 wherein A is COOH.
38. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 4~~, wherein the compound is selected from the group consisting of (2-Methyl-4-{2-[3-methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propylsulfanyl}-phenoxy)-acetic acid, (2-Methyl-4-{2-[3-methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propylsulfanyl}-phenoxy)-acetic acid, 3-(2-Methyl-4-{2-[3-methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propylsulfanyl}-phenyl)-propionic acid, and (3-{2-[3-Methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propoxy}-phenyl)-acetic.
39. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 4~~ that is (3-{2-[3-Methyl-5-(4-trifluoromethyl-phenyl)-thiophen-2-yl]-propoxy}-phenyl)-acetic.
40. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 4~~ wherein the compound is selected from the group consisting of
41. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 4~~ which is selected from the group consisting of {2-Methyl-4-[5-(4-trifluoromethyl-phenyl)-thiophen-2-ylmethoxy]-phenoxy}-acetic acid and 3-{2-Methyl-4-[5-(4-trifluoromethyl-phenyl)-thiophen-2-ylmethoxy]-phenyl}-propionic acid.
42. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 38~~ 11 which is the S conformation.
43. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 38~~ 11 which is the R conformation.

44. (Currently amended) A pharmaceutical composition, comprising as an active ingredient, at least one compound as claimed by ~~any one of Claims 1 through 43~~ 11 together with a pharmaceutically acceptable carrier or diluent.
45. (Cancel)
46. (Currently amended) A method of treating diabetes mellitus in a mammal, comprising the step of administering to the mammal in need thereof, a therapeutically effective amount of at least one compound of Claims ~~1 through 43~~ 11.
47. (Currently amended) A method of treating Metabolic syndrome in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims ~~1 through 43~~ 11.
48. (Currently amended) A method of selectively modulating a PPAR delta receptor comprising administering a compound as claimed by ~~any one of Claims 1 through 43~~ 11 to a mammal in need thereof.
49. (Cancel)
50. (Currently amended) A method of treating atherosclerosis in a mammal, comprising the step of administering to the mammal in need thereof a therapeutically effective amount of at least one compound of Claims ~~1 through 43~~ 11.
51. (Currently amended) A method for treating or preventing the progression of cardiovascular disease in a mammal in need thereof comprising administering a therapeutically effective amount of a compound as Claimed by ~~any one of Claims 1 through 43~~ 11.
52. (Original) A method as claimed by Claim 51 wherein the mammal is diagnosed as being in need of such treatment.
53. (Currently amended) A method of treating arthritis in a mammal, comprising the step of administering to the mammal in need thereof, a therapeutically effective amount of at least one compound as claimed by ~~any one of Claims 1 through 43~~ 11.
54. (Currently amended) A method of treating demyelating disease in a mammal, comprising the step of administering to the mammal in need

thereof, a therapeutically effective amount of at least one compound as claimed by ~~any one of Claims 1 through 43~~ 11.

55. (Currently amended) A method of treating inflammatory disease in a mammal, comprising the step of administering to the mammal in need thereof, a therapeutically effective amount of at least one compound as claimed by ~~any one of Claims 1 through 43~~ 11.

56. (Currently amended) A method as claimed by ~~any one of Claims 53, 54, and 55~~ wherein such mammal is diagnosed as being in need of such treatment.

57. (Currently amended) A compound as Claimed by ~~any one of Claims 1 through 43~~ 11 for use as a pharmaceutical.

58. (Currently amended) A compound as claimed by ~~any one of Claims 1 through 43~~ 11 wherein the compound is radiolabeled.

59. (Canceled)

60. (Canceled)